16. The method according to claim 11 wherein the at least one cholinesterase inhibitor is administered in an amount of from about 20 mg to about 200 mg per day.

A' cont

17. The method according to claim 11 wherein the patient suffering from Parkinson's disease suffers from parkinsonian dementia.

**REMARKS**

Claims 1-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Shapiro. The Examiner alleges that Shapiro teaches treatment of neurodegenerative diseases such as Parkinson's disease, Alzheimer's presenile and senile dementia using two or more therapeutic agents in combination, which yields supra activity. In Example I, Shapiro is said to teach treatment of Parkinson's disease by a combination of known medicaments with co-agents such as levodopa and tacrine. Shapiro is also said to teach cholinesterase inhibitors such as physostigmine, tacrine, metrofinate, and galanthamine and velancrine maleate.

This rejection is respectfully traversed. In disclosing that in the use of two-drug combinations for treating memory processing, Shapiro merely discloses that some combinations of drugs yielded supra-additivity. However, this is merely a disclosure in the prior art that there can be a synergistic value

of using two or more therapeutic agents in combination, as noted at column 1, lines 32-44. There is no disclosure of what specific drugs can be combined to obtain this supra-activity.

Shapiro's invention is for treating neurological diseases using carbonyl trapping agents in combination with other drugs. Shapiro, U.S. Patent No. 5,668,117, is a continuation in part application of Serial No. 26,617, filed February 23, 1993, which is a continuation of Serial No. 660,561, filed February 22, 1991, both of which appear to be directed to the carbonyl trapping agents alone. Shapiro's invention, then, is the combination of a carbonyl trapping agent with another, allegedly conventional, drug for treating neurological diseases. Shapiro never contemplates using drugs in the absence of the carbonyl trapping agents.

Shapiro discloses at column 28, lines 30-40 and column 30, lines 1-4, that clinical treatment of Parkinson's disease may be improved by the use of the invention originally disclosed in U.S. Patent application Serial No. 07/660,561, that is, with the carbonyl trapping agents, in combination with known medicaments, including co-agent use of levodopa and tacrine. Shapiro never even suggests that it has been known to use tacrine to treat Parkinson's disease, only that the carbonyl trapping agents can be used in combination with tacrine to treat Parkinson's disease.

In Example 2, Shapiro discloses that clinical treatment of Alzheimer's disease may be improved by the use of the invention originally disclosed in U.S. Patent application Serial. No. 07/660,561, notably, the carbonyl trapping agents, in combination with known medicaments, including acetylcholinesterase inhibitors.

Again, Shapiro only discloses using the carbonyl trapping agents in combination with the acetylcholinesterase inhibitors for treating Alzheimer's disease.

In both Examples 1 and 2, Shapiro has provided a shotgun enumeration of drugs that can be used in combination with the carbonyl trapping agent to treat neurological disease. However, Shapiro never recognizes that a cholinesterase inhibitor such as tacrine *per se* can be used successfully to treat Parkinson's disease, either alone or in combination with levodopa.

In fact, it was completely unexpected that a cholinesterase inhibitor could be used to treat Parkinson's disease, even though tacrine, a cholinesterase inhibitor, was one of the first drugs approved for treating Alzheimer's disease. Alzheimer's disease and Parkinson's disease, while both being neurological diseases, are not the same, and are not amenable to the same treatment. In fact, as will be demonstrated below, cholinesterase inhibitors were contraindicated for treating Parkinson's patients, as central cholinergic activity appears to be important for memory function in Parkinson's disease.

Prior to the introduction of levodopa, anticholinergic drugs had been the conventional treatment for mild parkinsonism since the discovery of belladonna alkaloids in the mid-nineteenth century. However, these drugs had a propensity for exacerbating dementia. Nevertheless, since anticholinergic drugs are known to ameliorate rigidity in the early stages of the disease, the conventionally skilled neurologist would instinctively believe that a procholinergic drug might worsen rigidity, as central

cholinergic activity appears to be important for memory function in Parkinson's disease. Unfortunately, patients receiving anticholinergic drugs for parkinsonism may experience reversible cognitive deficits so severe as to mimic Alzheimer's disease. Identical memory disturbances have been produced by administration of atropine to patients with either Alzheimer's disease or Parkinson's disease with dementia.

Although dementia may be associated with Parkinson's disease, Alzheimer's disease and Parkinson's disease are pathologically very distinct. Senile dementia of the Alzheimer type (SDAT) is associated with degeneration of the nucleus basalis, and consequently with a cholinergic deficit. Thus, cholinesterase inhibitors are logical drugs to try for treating Alzheimer's disease. Alzheimer's disease is characterized by plaques and neurofibrillar tangles, mainly in the cerebral cortex.

Parkinson's disease, on the other hand, is characterized by distinctive Lewy bodies, which are eosinophilic, cytoplasmic structures found mainly in small nuclei at the base of the brain, especially the substantia nigra (dopaminergic cells) and nucleus basalis. Alzheimer's disease and Parkinson's disease are clinically distinguishable to a competent practitioner.

Clinically, Alzheimer's disease presents with personality change, language errors (difficulties with categorical speed and word generation) and loss of short term memory. The patient is usually alert and attentive. The condition may or may not progress to include mild rigidity of the muscles, although rigidity is never the presenting complaint.

Parkinson's disease, in contrast, presents with muscular rigidity, tremor and imbalance. It may or may not progress to include dementia. However, dementia is never the presenting complaint. When dementia is present in Parkinson's patients, it is clinically distinguishable from Alzheimer's disease, and is characterized by inattention, visual hallucinations, and a worsening of the confusion produced by administration of levodopa.

Recent trials using cholinesterase inhibitors, such as tacrine, have shown promise for partial reversal of senile dementia of the Alzheimer type in a few patients. Ott et al., in Clinical Neuropharmacology 15(4): 322-325, 1992, a copy of which is submitted herewith, treated a patient with Alzheimer's disease with tacrine, which has traditionally been used to treat Alzheimer's dementia. The individual originally presented as Alzheimer's disease developed other symptoms, including extrapyramidal features. This patent, along with three other patients with a typical presentation of Alzheimer's disease, responded with improvement or stabilization in cognitive ability and activities of daily living score. Another case, again clinically and neuropathologically diagnosed as Alzheimer's disease, responded initially, but this response was not sustained.

Ott et al. thus clearly imply that increasing rigidity would be expected in a Parkinson patient to whom tacrine is administered, since the tacrine administered caused rigidity in an Alzheimer's patient. This would certainly deter a practicing

neurologist from prescribing this type of medication for a patient suffering from Parkinson's disease, since any medication that increases rigidity would be contraindicated for parkinsonian patients. Moreover, Ott et al. state on page 325 that central cholinergic activity appears to be important for memory function in Parkinson's disease. Patients receiving anticholinergic drugs for parkinsonism may experience reversible cognitive deficits so sever as to mimic Alzheimer's disease.

Treatment of dementia in parkinsonian patients with cholinometric drugs presents a dilemma, since the movement disorder characteristic of Parkinson's disease would be expected to worsen with treatment with tacrine or similar anticholinesterase medications. It should be noted that Ott et al., ibid, treated an Alzheimer's patient with mild parkinsonism, rather than a patient whose primary presentation was Parkinson's disease, with a combination of levodopa and tacrine. The dramatic increase in tremors, as well as induction of gait dysfunction and subjective feelings of rigidity, were attributed to the cholinergic effects of acetylcholinesterase inhibitors on the striatum. The increased tremor responded to addition of levodopa as well as to a decrease in the tacrine dosage, with restoration of baseline function after either maneuver.

Perry et al., in Annals New York Academy of Sciences pp. 197-202, a copy of which is submitted herewith, report examining cholinergic and monoaminergic (dopaminergic and serotoneric) activities in postmortem brain tissue in senile dementia of Lewy body type, Parkinson's disease, and Alzheimer's disease. The

quantitative data they obtained suggested that although extra-pyramidal symptoms relate to striatal levels of dopamine, cognitive impairment was most closely associated with cholinergic but not monoaminergic deficits in temporal and archicortical areas. For example, hallucinations, frequently manifested in Lewy body dementia, appear to be related to an extensive cholinergic deficit in temporal neocortex and the resulting imbalance between decreased cholinergic and relatively preserved serotonergic activities.

As with Lewy body dementia, Parkinson's disease is associated with a cholinergic deficit, which may be more profound that that seen in senile dementia of the Alzheimer type. As anticholinergic drugs have mild antiparkinsonian effects, however, it has been assumed that a procholinergic drug will worsen the characteristic rigidity of Parkinson's disease. However, as can readily be seen from the examples given in the instant specification, beginning at page 14, last paragraph, the subjects treated with cholinesterase inhibitors exhibited marked changes in their physical conditions, with the patients able to walk independently, with improvements in gait corresponding roughly to improvements in mentation. Thus, the cholinesterase inhibitors were effective in treating the motor dysfunction of Parkinson's disease, which would be <u>wholly</u> <u>unexpected</u> from the Ott et al. disclosure which showed increased rigidity in Alzheimer's patients treated with tacrine.

From the above, it can clearly be seen that a drug that is effective in treating Alzheimer's dementia may be detrimental to a patient suffering from Parkinson's disease. Thus, despite the shotgun listing of possible drugs to use in combination with carbonyl trapping agents for treating neurological diseases, there is nothing in Shapiro that refutes the conventional wisdom that administering a procholinergic drug to a patient suffering from Parkinson's disease is contraindicated, nor is there anything in Shapiro that even suggests, much less teaches, that administering a cholinesterase inhibitor in the absence of a carbonyl trapping agent can be used to treat Parkinson's disease.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shapiro. The Examiner concedes that Shapiro does not teach the latter compounds for Parkinson's dementia, but still concludes that it would have been obvious to one of ordinary skill in the art to use the cholinesterase inhibitors taught by Shapiro to treat Parkinson's dementia, because in the absence of evidence otherwise, the teachings of Shapiro include Parkinson's dementia.

This rejection is respectfully traversed. One skilled in this particular art is a neurologist, who treats Alzheimer's patients, Parkinson's patients, or both. As noted above, there is sufficient evidence that would lead one skilled in the art of treating Parkinson's patients, i.e., a neurologist, to avoid treating these patients with a cholinesterase inhibitor, as there would be the danger of worsening the rigidity of Parkinson's

disease. Moreover, since Parkinson's dementia is not clinically the same as Alzheimer's disease, there is no reason to believe that the treatment for the two diseases would be the same.

There is nothing in Shapiro or in the literature to suggest to one skilled in the art that a compound which is useful for treating Alzheimer's disease would be useful in treating Parkinson's disease. One example of this is the use of tocopherol, in which an article in the New England Journal of Medicine 328 176-83 (1993) by the Parkinson's Disease Study Group reported that tocopherol had no effect on the progression of symptoms in Parkinson's disease. However, Sano et al., in the New England Journal of Medicine 336 1216-22 (1997) shows that tocopherol slows the progression of symptoms in Alzheimer's disease. Thus, simply because a compound is effective in treating Alzheimer's disease does not suggest to one skilled in the art that the compound would be useful in treating Parkinson's disease.

While Shapiro does indeed teach treating Parkinson's disease, Shapiro treats Parkinson's disease with a combination of a carbonyl trapping agent and another medicament. It should be noted from the abstract that Shapiro states that the compositions are used to treat a mammal suffering from a neurological disease characterized by covalent bond crosslinking between the nerve cells, other cellular structures, and their intracellular and extracellular components. This definition includes Alzheimer's disease, but, as demonstrated above, does not include Parkinson's

disease. Therefore, it is questionable whether Shapiro even intended to treat Parkinson's disease per se with his carbonyl trapping agents.

The present inventor has discovered that cholinesterase inhibitors, despite conventional wisdom among neurologists, are indeed effective in treating the motor dysfunction of Parkinson's disease along with the dementia. There is nothing in Shapiro that refutes this conventional wisdom for treating Parkinson's disease and therefore would lead one skilled in the art to treat Parkinson's disease with a cholinesterase inhibitor.

In view of the above, it is respectfully submitted that the claims are now in condition for allowance, and favorable action thereon is earnestly solicited.

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# A CONTROLLED TRIAL OF SELEGILINE, ALPHA-TOCOPHEROL, OR BOTH AS TREATMENT FOR ALZHEIMER'S DISEASE

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## ABSTRACT

***Background*** There is evidence that medications or vitamins that increase the levels of brain catecholamines and protect against oxidative damage may reduce the neuronal damage and slow the progression of Alzheimer's disease.

***Methods*** We conducted a double-blind, placebo-controlled, randomized, multicenter trial in patients with Alzheimer's disease of moderate severity. A total of 341 patients received the selective monoamine oxidase inhibitor selegiline (10 mg a day), alpha-tocopherol (vitamin E, 2000 IU a day), both selegiline and alpha-tocopherol, or placebo for two years. The primary outcome was the time to the occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3).

***Results*** Despite random assignment, the base-line score on the Mini-Mental State Examination was higher in the placebo group than in the other three groups, and this variable was highly predictive of the primary outcome ($P<0.001$). In the unadjusted analyses, there was no statistically significant difference in the outcomes among the four groups. In analyses that included the base-line score on the Mini-Mental State Examination as a covariate, there were significant delays in the time to the primary outcome for the patients treated with selegiline (median time, 655 days; $P=0.012$), alpha-tocopherol (670 days, $P=0.001$), or combination therapy (585 days, $P=0.049$), as compared with the placebo group (440 days).

***Conclusions*** In patients with moderately severe impairment from Alzheimer's disease, treatment with selegiline or alpha-tocopherol slows the progression of disease. (N Engl J Med 1997;336:1216-22.)



ALZHEIMER'S disease is a neurodegenerative disorder characterized by loss of memory and other cognitive abilities. Neuropathologically, the disease is characterized by the presence of neurofibrillary tangles and senile plaques, impaired synaptic function, and cell loss.[1] There is a prominent loss of cholinergic, noradrenergic, and dopaminergic neurons in Alzheimer's disease.[2] The pathology of the disorder may involve oxidative stress and the accumulation of free radicals, leading to excessive lipid peroxidation and neuronal degeneration in the brain.[3-6]

Selegiline, a monoamine oxidase inhibitor, and alpha-tocopherol may have beneficial effects in patients with Alzheimer's disease. Selegiline may act as an antioxidant, since it inhibits oxidative deamination, thereby reducing neuronal damage. The drug has been associated with an increased active life span in animals.[7] Studies in patients with Parkinson's disease have demonstrated that selegiline delays the need for dopamine-replacement therapy and significantly prolongs the time during which patients function well enough to work.[8]

Selegiline also increases levels of catecholamines, and adrenergic stimulation may improve the cognitive deficits associated with Alzheimer's disease. In short-term trials of selegiline in patients with Alzheimer's disease, small but significant improvements in cognition[9] and overall ratings of functioning[10] have been reported. A longer study with a small sample yielded a similar but nonsignificant trend.[11]

Alpha-tocopherol (vitamin E) is a lipid-soluble vitamin that interacts with cell membranes, traps free radicals, and interrupts the chain reaction that damages cells.[12] In animal models, alpha-tocopherol reduced the degeneration of hippocampal cells after cerebral ischemia[13] and enhanced the recovery of motor function after spinal cord injury.[14] In hypoxic cultured neurons, alpha-tocopherol inhibited lipid peroxidation[15] and reduced cell death associated with β-amyloid protein.[16] Although no benefit was noted in a study of alpha-tocopherol in patients with Parkinson's disease,[8] there is much interest in a possible role of antioxidants in delaying the onset of Alzheimer's disease.

The primary purpose of the present study was to determine whether selegiline, alpha-tocopherol, or a

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*The members of the Alzheimer's Disease Cooperative Study are listed in the Appendix.

combination of the two agents would slow the clinical deterioration associated with Alzheimer's disease. Although previous trials involving patients with Alzheimer's disease have focused on cognitive deterioration, our study examined functional loss. We sought to determine whether treatment with these agents could delay the time to the occurrence of clinical outcomes that reflect substantial functional deterioration.

## METHODS

Patients were recruited from 23 centers participating in the Alzheimer's Disease Cooperative Study (see the Appendix). A total of 341 patients with probable Alzheimer's disease of moderate severity, as measured by a Clinical Dementia Rating of 2,[17] were enrolled. Informed consent was obtained from each patient or a family member. At the time of enrollment, the patients were free of other central nervous system diseases, were not taking psychoactive medications, and were residing either at home or in a supervised setting with a care giver but not in a skilled-nursing facility. The study population has been described in detail previously.[18]

The patients were randomly assigned (after stratification according to center with the use of a permuted-block procedure) to receive selegiline, alpha-tocopherol, selegiline and alpha-tocopherol, or placebo. Selegiline (Eldepryl, Somerset Pharmaceuticals, Tampa, Fla.) was given in a dose of 5 mg twice a day, and a racemic mixture of *dl*-alpha-tocopherol (vitamin E, Hoffmann-LaRoche, Nutley, N.J.) was given in a dose of 1000 IU twice a day; both agents were given in the morning and in the afternoon.

### Primary Outcome Measure

The primary outcome measure was the time to the occurrence of any one of the following end points: death; institutionalization; loss of the ability to perform at least two of three basic activities of daily living (i.e., eating, grooming, using the toilet), as measured by part 2 of the Blessed Dementia Scale[19]; and severe dementia, defined as a Clinical Dementia Rating of 3.[17] The date of death or institutionalization was used to calculate the time to either of these end points; if that date was not available, the date of the next follow-up visit was used. To calculate the time to the loss of the ability to perform activities of daily living or the occurrence of severe dementia, we used the date of the follow-up visit during which the end point was documented.[14]

Secondary outcome measures included measures of cognition, function, behavior, and the presence or absence of extrapyramidal signs. Cognition was assessed with the cognitive portion of the Alzheimer's Disease Assessment Scale[20] and the Mini–Mental State Examination.[21] Function was assessed with the total score on the Blessed Dementia Scale. This scale has two sections: instrumental activities of daily living (e.g., remembering lists and handling small sums of money) and basic activities of daily living (e.g., eating, using the toilet, and grooming). Function was also assessed with the Dependence Scale, a seven-point scale that rates the need for supervision and care.[22] The Equivalent Institutional Service, a subsection of the Dependence Scale, rates the level of care received as follows: 1, limited home care; 2, care equivalent to that received in an adult care facility; and 3, care equivalent to that received in a skilled-nursing facility. Behavioral disturbance was assessed with the Behavior Rating Scale for Dementia.[23] Extrapyramidal signs were assessed with a modification of the motor part of the Unified Parkinson's Disease Rating Scale.[24] A score of 2 or higher on any item was considered to indicate the presence of extrapyramidal signs.

### Safety

To assess the safety of treatment, routine blood and urine analyses were performed and vital signs and weight were checked at all clinic visits. Medical events that occurred during the treatment period were reported as adverse events. These events were categorized on the basis of the description provided.

### Follow-up

Assessments were conducted one month after enrollment and at three-month intervals for the remainder of the two-year study period. At each interval, every effort was made to assess primary and secondary outcomes, regardless of whether an end point had been reached or the medication had been discontinued.

### Drug-Level Monitoring

The level of alpha-tocopherol was monitored by measuring serum tocopherol concentrations, and the level of selegiline was monitored by measuring amphetamine, its major metabolite, in urine. Tests for selegiline were considered positive if the presence of amphetamine was detected in 75 percent of the urine samples obtained from a given patient. Tests for alpha-tocopherol were considered positive if serum tocopherol levels were 2.0 mg per deciliter (46 μmol per liter) or higher in 75 percent of the blood samples obtained from a given patient.

### Statistical Analysis

Base-line differences in predetermined potential covariates among the four groups were examined with the use of either analysis of variance or chi-square analyses, as appropriate. The variables examined included demographic characteristics (age, duration of illness, education, and sex) and clinical characteristics (scores on the Mini–Mental State Examination and Blessed Dementia Scale and the presence or absence of extrapyramidal signs). The variables that differed significantly among the groups at the 0.1 level were examined as predictors of the primary outcome, and the significant predictors were included in the analysis of the treatment effect.

The primary intention-to-treat analysis of treatment efficacy compared each treatment with placebo with the use of a Kaplan–Meier estimation[25] and log-rank testing for the unadjusted analysis and the Cox proportional-hazards model to control for any imbalance in the predetermined covariates among the four groups. The relative risk associated with treatment as compared with placebo was measured with the use of the risk ratio derived from the Cox model, with significance levels adjusted for multiple comparisons.[26] The median time to an end point was estimated on the basis of survival curves generated from the Cox model.

The secondary outcomes were examined with the use of survival analyses, analysis of variance, or analysis of covariance, as appropriate. Missing values were imputed by using the last observation carried forward. For each of these analyses, the rate of study completion was compared among the four groups. If significant differences were observed ($P \leq 0.1$), the time enrolled in the study was included as a covariate in the model.

Safety data were examined by using Fisher's exact test to compare the frequency of abnormal findings (e.g., adverse events or abnormalities in laboratory results or vital signs) among the study groups.

A safety-monitoring committee reviewed the safety data coded according to the study group or uncoded, as needed. The committee was responsible for recommending changes in the protocol or early termination of the study, if necessary. A preplanned interim analysis was conducted at the midpoint of the study, with prespecified rules for termination.[27] Log-rank tests were used for the unadjusted analysis, and the Cox model was used to adjust for age, score on the Mini–Mental State Examination, and sex. No significant treatment effects were observed in the interim analysis.

## RESULTS

Table 1 shows the demographic and clinical characteristics of each study group at base line. There

TABLE 1. BASE-LINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 341 PATIENTS WITH ALZHEIMER'S DISEASE RANDOMLY ASSIGNED TO RECEIVE PLACEBO, SELEGILINE, ALPHA-TOCOPHEROL, OR BOTH AGENTS.*

| CHARACTERISTIC | PLACEBO (N=84) | SELEGILINE (N=87) | ALPHA-TOCOPHEROL (N=86) | SELEGILINE AND ALPHA-TOCOPHEROL (N=88) |
|---|---|---|---|---|
| Age (yr) | 73.5±8.3 | 72.7±8.9 | 73.4±7.8 | 73.9±7.1 |
| Education (yr) | 12.2±3.1 | 12.4±3.7 | 12.6±3.3 | 12.7±3.3 |
| Duration of illness (yr) | 5.5±2.9 | 4.8±2.4 | 5.3±2.7 | 4.7±2.5 |
| Female sex (% of patients) | 65.5 | 67.8 | 65.9 | 60.0 |
| Score on Mini–Mental State Examination† | 13.3±4.9‡ | 12.7±5.0 | 11.3±5.7 | 12.9±5.7 |
| Score on Blessed Dementia Scale§ | 6.1±2.1 | 6.3±1.9 | 6.6±2.1 | 6.4±2.3 |
| Extrapyramidal signs (% of patients) | 19.0 | 26.4 | 18.8 | 24.7 |
| Clinical Dementia Rating¶ | 10.9±1.2 | 11.0±1.2 | 11.3±1.3 | 10.9±1.2 |

*Plus–minus values are means ±SD.

†Possible scores range from 0 (worst) to 30 (best).

‡F = 2.37; df = 3336; P = 0.071, for the comparison between the placebo group and the other three groups.

§Possible scores range from 0 (best) to 17 (worst).

¶Scores shown represent the total of the scores in six domains of the Clinical Dementia Rating.[17] Possible summary scores range from 0 (best) to 18 (worst).

was a trend toward a significant difference among the groups in the score on the Mini–Mental State Examination (P = 0.071), with the placebo group having the highest score and the alpha-tocopherol group having the lowest score. There were no significant differences in the other variables. In the Cox model, a higher score on the Mini–Mental State Examination was strongly associated with a delay in the primary outcome (risk ratio, 0.909 per unit increase in score; P<0.001) and was also associated with a delay in each of the individual outcomes.

### Primary Outcome Measure

The results of unadjusted comparisons of selegiline with placebo (risk ratio, 0.72; P = 0.087), alpha-tocopherol with placebo (risk ratio, 0.70; P = 0.077), and combined treatment with placebo (risk ratio, 0.78; P = 0.21) were not statistically significant (Fig. 1A, 1B, and 1C). However, when the base-line score on the Mini–Mental State Examination was included as a covariate (Fig. 1D), a significant delay in the primary outcome was found with selegiline (risk ratio, 0.57; P = 0.012), alpha-tocopherol (risk ratio, 0.47; P = 0.001), and combination therapy (risk ratio, 0.69; P = 0.049). The estimated increase in median survival was 230 days for the patients receiving alpha-tocopherol, 215 days for those receiving selegiline, and 145 days for those receiving both, as compared with the patients receiving placebo (Table 2).

We also examined the effect of treatment on each of the individual end points in the primary outcome measure (Table 3). For the end point of institutionalization, the comparison of alpha-tocopherol with placebo showed a significant treatment effect (risk ratio, 0.42; P = 0.003). No statistically significant differences among the groups were observed for the other end points.

### Secondary Outcome Measures

The results of the analyses of secondary outcome measures are presented in Table 4. In some cases, the cognitive data were not complete because of the development of advanced dementia. The mean time to the last score on the Mini–Mental State Examination was 15.6 months, and the scores did not differ significantly among the four groups. Changes from the base-line scores also did not differ significantly among the groups (P = 0.83).

The change in the performance on the cognitive portion of the Alzheimer's Disease Assessment Scale was calculated as the difference between the base-line score and the score at the last visit. The mean time to the last score was 12.4 months. The changes in the scores did not differ significantly among the four groups (P = 0.17). The use of the base-line score on the Mini–Mental State Examination and the time in the study as covariates did not change these results.

For the Blessed Dementia Scale, the mean time to

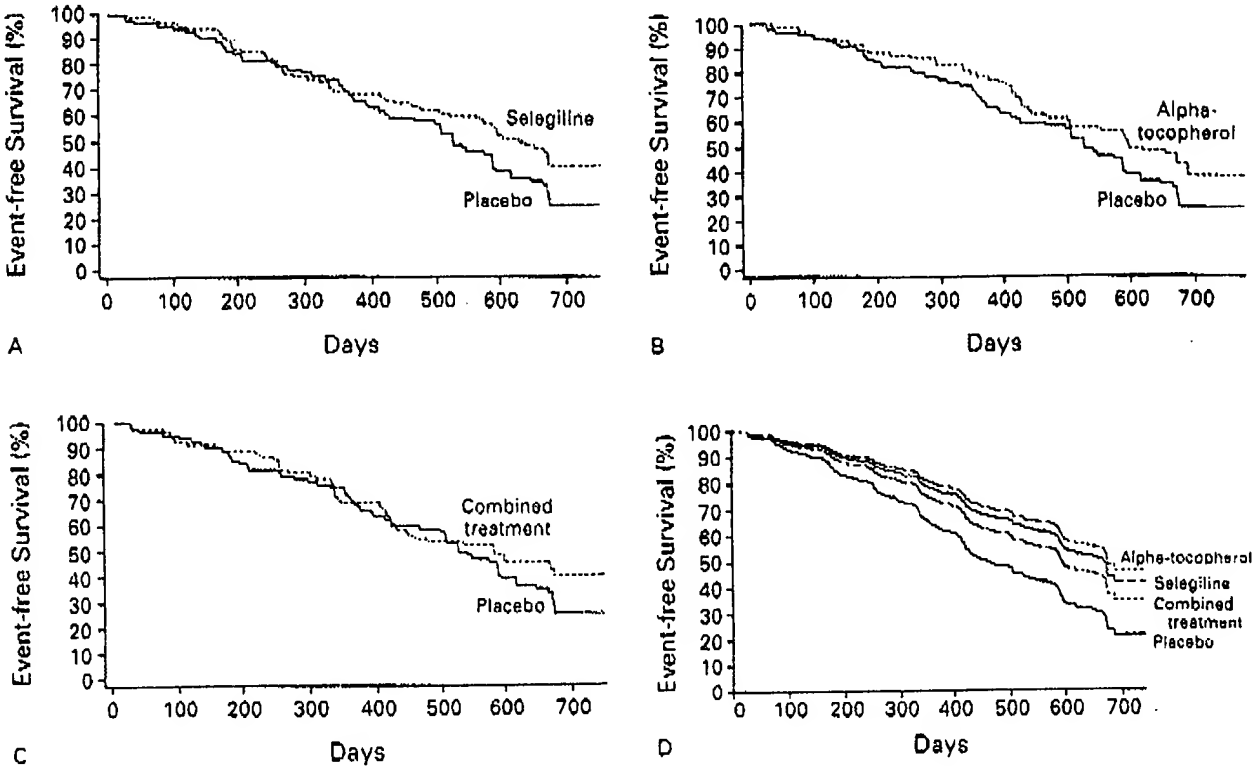


**Figure 1.** Event-free Survival of 341 Patients with Alzheimer's Disease Assigned to Treatment with Selegiline, Alpha-Tocopherol, Both, or Placebo.

Event-free survival was defined as survival until the occurrence of death, institutionalization, loss of the ability to perform the activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3). Panels A, B, and C show Kaplan–Meier curves for the comparison of placebo with selegiline ($P=0.087$), alpha-tocopherol ($P=0.077$), and combined treatment ($P=0.21$), respectively. Panel D shows a Cox-model estimation for the comparison of the three treatments with placebo, with the base-line score on the Mini–Mental State Examination included as a covariate ($P=0.012$, 0.001, and 0.049, respectively).

the last observation was 20.0 months. The change in the score from base line to the last evaluation differed significantly among the groups ($P=0.004$), with the base-line score on the Mini–Mental State Examination included as a covariate. Pairwise post hoc comparisons showed significant differences between each treatment group and the placebo group, with a benefit associated with treatment.

At base line, 3 percent of the patients received the maximal rating of 3 for level of care. For the 331 patients who were not at level 3 at base line, similar proportions in the four groups received higher ratings at the last evaluation.

At base line, 3 percent of the patients had a maximal dependence level, defined as the need for assistance with moving, turning, eating, or using the toilet. For the 332 patients who were not at the maximal level at base line, the Cox model demonstrated a significant overall effect of treatment in maintaining a lower level of dependence ($P=0.039$). Patients treated with alpha-tocopherol alone or combined with selegiline required significantly less supervision than those receiving placebo ($P=0.021$ and 0.014, respectively).

Changes in the scores on the Behavioral Rating Scale for Dementia differed significantly among the four groups ($P=0.020$). The patients receiving combined therapy had a decrease in behavioral symptoms, whereas those receiving placebo had an increase in symptoms. The results of no other comparisons were significant.

Extrapyramidal signs were present at base line in 22 percent of the patients, with no significant differences among the four groups. There were no differences in the frequency of new extrapyramidal signs among the groups ($P=0.59$).

### Safety Data

A total of 49 categories of adverse events were defined. There were significant differences among the groups in three categories: dental events, which were defined as any event that led to dental treatment

TABLE 2. PRIMARY OUTCOME AND MEDIAN SURVIVAL ACCORDING TO STUDY GROUP.*

| PRIMARY OUTCOME AND SURVIVAL | PLACEBO (N=84) | SELEGILINE (N=87) | ALPHA-TOCOPHEROL (N=85) | SELEGILINE AND ALPHA-TOCOPHEROL (N=85) |
|---|---|---|---|---|
| Lost to follow-up — no. of patients (%)† | 6 (7) | 4 (5) | 8 (9) | 5 (6) |
| Primary outcome — no. of patients (%) | 58 (69) | 47 (54) | 45 (53) | 47 (55) |
| Unadjusted median survival (days) | 526 | 628 | 597 | 581 |
| Unadjusted difference in survival, treatment vs. placebo (days) | — | 102 | 71 | 55 |
| Estimated median survival (days) | 440 | 655 | 670 | 585 |
| Estimated difference in survival, treatment vs. placebo (days) | — | 215 | 230 | 145 |

*Estimates of survival are derived from the Cox model, with adjustment for the base-line score on the Mini–Mental State Examination. Survival was defined as the time to the primary outcome.

†Patients lost to follow-up were those who did not reach an end point and did not complete the study.

TABLE 3. PERCENTAGE OF PATIENTS REACHING EACH END POINT, ACCORDING TO STUDY GROUP.

| END POINT | PLACEBO | SELEGILINE | ALPHA-TOCOPHEROL | SELEGILINE AND ALPHA-TOCOPHEROL |
|---|---|---|---|---|
| | % of patients | | | |
| Loss of ability to perform activities of daily living | 31 | 28 | 22 | 28 |
| Clinical Dementia Rating of 3 | 51 | 43 | 48 | 47 |
| Institutionalization | 39 | 33 | 26 | 35 |
| Death | 12 | 10 | 12 | 7 |

(P=0.023); falls (P=0.005); and syncopal episodes (P=0.031) (Table 5). The frequency of other adverse events, including cardiac, gastrointestinal, dermatologic, and psychiatric or other neurologic symptoms, did not differ significantly among the groups. Overall, there were no statistically significant differences among the groups in adverse-event categories after adjustment for multiple comparisons.[16] There were also no significant differences in vital signs, weight change, or laboratory values among the groups.

The death rate was 10.3 percent, which is similar to that reported in another cohort of patients with Alzheimer's disease of the same severity.[17] We also examined the cause of death and found no specific pattern associated with treatment.

### Drug-Level Monitoring

Urine samples were available from 318 patients for analysis of amphetamine levels. The proportion of patients with positive tests for selegiline was 93 percent in the combined group, 98 percent in the selegiline group, 11 percent in the alpha-tocopherol group, and 13 percent in the placebo group. Serum samples were available from 332 patients. The proportion of patients with positive tests for alpha-tocopherol was 91 percent in the combined group, 93 percent in the alpha-tocopherol group, 9 percent in the selegiline group, and 12 percent in the placebo group.

## DISCUSSION

In this double-blind, controlled study of patients with Alzheimer's disease, treatment with selegiline or alpha-tocopherol or both was beneficial in delaying the primary outcome of disease progression. The median time to the primary outcome was longer with each treatment than with placebo. There was a trend toward a delay in reaching each of the individual end points making up the primary outcome, with a significant delay in institutionalization in the alpha-tocopherol group. There were also significant delays in the deterioration of the performance of activities of daily living and the need for care. These findings should be of interest since, to date, no treatment for Alzheimer's disease has shown similar benefits with respect to these outcomes. The possibility that our findings reflect aberrations in the placebo group is unlikely, since the patients in this group reached the end points at the same rate as patients in other multicenter studies.[18]

Falls and syncope were more frequent in the treatment groups, especially the group receiving combined treatment, than in the placebo group. Although similar results have been reported with selegiline, there are no such reports with alpha-tocopherol, and the reason for the increased numbers of falls and syncopal episodes in the group receiving combined treatment is unclear. However, these events did not lead to the discontinuation of treatment, and we conclude that each agent alone may be relatively well tolerated by patients with Alzheimer's disease.

There were no demonstrable differences between the results in the group receiving combined treatment and either of the groups receiving individual treatment. There are several possible explanations for the lack of an additive effect of treatment. Perhaps both agents exert their effects through the same mechanism, with either agent providing a maximal benefit. Alternatively, each agent may work through an independent mechanism, but the disease may have been sufficiently severe that no additive benefit could be observed. Finally, one agent may interfere with the absorption or metabolism of the other, resulting in an effect that is not additive.

Our findings suggest that the use of selegiline or

alpha-tocopherol may delay clinically important functional deterioration in patients with Alzheimer's disease. One can only speculate about the mechanism underlying this effect. Selegiline may have enhanced the functioning of nigral neurons or enhanced their survival by inhibiting oxidative deamination. Alpha-tocopherol may have provided the same benefit, resulting in the inability to observe an additive effect in the group receiving combined treatment.

In our study, there was no improvement in cognitive test scores in any of the treatment groups. Our patients were more severely impaired than those described in other clinical trials,[28,29] and our observation period was long, with a large proportion of patients who did not complete the two years of testing. However, even when we controlled for the length of the observation period, treatment had no effect on cognitive scores. The observed changes in the scores on the cognitive portion of the Alzheimer's Disease Assessment Scale and the Mini-Mental State Examination are similar to those reported in other studies,[30] and our findings do not suggest that the patients had reached a maximal deficit. It is possible that other features of advanced disease (e.g., behavioral disturbances and functional impairments) make it difficult to assess the cognitive domain. Although cognitive measures have typically been the index of symptomatic improvement measured over a short interval, they may not be the best measures of disease progression, particularly in a cohort of patients with moderately severe Alzheimer's disease followed for a long interval. There was a benefit of treatment associated with the score on the Blessed Dementia Scale, which includes instrumental activities of daily living — those that require cognitive function. Perhaps functional and occupational measures of cognitive capacity are better indicators of disease progression than psychometric measures.

The role of selegiline and alpha-tocopherol in the treatment of neurodegenerative diseases is currently of great interest. Selegiline delays the onset of disability in patients with Parkinson's disease.[8] Previous trials of alpha-tocopherol have demonstrated no benefit in patients with Huntington's disease[31] or Parkinson's disease.[8] The neuronal populations involved in Alzheimer's disease are more sensitive to oxidative stress than those in other neurodegenerative diseases. Perhaps these neurons mediate the clinical end points described here. The outcome of improved function despite the absence of improved cognition raises the possibility that the effect we observed is a nonspecific health benefit to which our primary outcome was sensitive. For example, in elderly populations it has been suggested that antioxidants improve cardiovascular function[32] and the immune response[33] and also reduce the risk of cancer.[34] Although we found no differences in the frequency of these types of adverse events in our study groups, we have no biologic data to evaluate these possible effects. The small behavioral effect that we observed is unlikely to account for these results. Perhaps cognitive measures would be sensitive to changes at earlier stages of the disease. However, only randomized clinical trials can determine the usefulness of these agents in other populations.

Both selegiline and alpha-tocopherol delay functional deterioration, particularly as reflected by the need for institutionalization, and should be consid-

TABLE 4. SECONDARY OUTCOME MEASURES.

| OUTCOME MEASURE* | PLACEBO | SELEGILINE | ALPHA-TOCOPHEROL | SELEGILINE AND ALPHA-TOCOPHEROL |
|---|---|---|---|---|
| Mini-Mental State Examination (mean change in score) | −4.6 | −5.1 | −4.6 | −4.9 |
| Alzheimer's Disease Assessment Scale (mean change in score) | 6.7 | 8.3 | 8.3 | 6.6 |
| Blessed Dementia Scale (mean change in score) | 5.4 | 4.2† | 4.0† | 4.2† |
| Equivalent Institutional Service (% of patients receiving higher rating) | 59 | 57 | 57 | 56 |
| Dependence Scale (% of patients receiving higher score) | 86 | 80 | 76‡ | 76‡ |
| Behavior Rating Scale for Dementia (mean change in score) | 8.9 | 5.4 | 4.4 | −1.1§ |
| Unified Parkinson's Disease Rating Scale (% of patients with new extrapyramidal signs) | 57 | 61 | 58 | 52 |

*For the Mini-Mental State Examination, a lower number indicates worse performance. For all other measures, a higher number indicates worse performance.

†P=0.004 for the comparison with placebo.

‡P=0.039 for the comparison with placebo.

§P=0.020 for the comparison with placebo.

TABLE 5. FREQUENCY OF ADVERSE EVENTS ACCORDING TO STUDY GROUP.

| ADVERSE EVENT | PLACEBO | SELEGILINE | ALPHA-TOCOPHEROL | SELEGILINE AND ALPHA-TOCOPHEROL | P VALUE* |
|---|---|---|---|---|---|
| | no. of patients (%) | | | | |
| Dental event | 0 | 6 (7) | 1 (1) | 1 (1) | 0.023 |
| Fall | 4 (5) | 8 (9) | 12 (14) | 19 (22) | 0.005 |
| Syncope | 3 (4) | 9 (10) | 6 (7) | 14 (16) | 0.031 |

*P values are for the comparison of each treatment with placebo.

ered for use in patients with moderate dementia. Convenience and cost may play a part in treatment decisions, since both agents were effective. It should be noted that statistically significant results were seen in a model that included adjustment for the base-line differences among the groups in the score on the Mini–Mental State Examination. Although this type of adjustment was used in other studies of drugs to treat Alzheimer's disease,[28,29] it may limit the interpretation of these results. Replication of our findings would lend support to our data showing the efficacy of these agents. In addition, little is known about the efficacy of these compounds in other patients, such as those with mild cognitive impairment, early dementia, or the very late stages of Alzheimer's disease.

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## APPENDIX

The following members of the Alzheimer's Disease Cooperative Study participated in this study: S. Vicari, Southern Illinois University, Springfield; D. Bennett, C. Forchetti, and A. Levin, Rush Institute on Aging, Chicago; C. Clark, University of Pennsylvania, Philadelphia; K. Davis, P. Aisen, D. Marin, and R. Mohs, Mount Sinai School of Medicine, New York; R. Doody, E. Lipscomb, and P. Schulz, Baylor College of Medicine, Houston; S. Ferris, E. Resnick, and T. McRae, New York University Medical Center, New York; N. Foster, N. Barbas, L. Bieliauskas, and L. Bluemlein, University of Michigan, Ann Arbor; J. Growdon, N. Simonian, M. Tennis, C. Burke, A. Markus, and K. Graefe, Massachusetts General Hospital, Boston; L. Harrell, University of Alabama at Birmingham, Birmingham; C. Kawas, H. Karagiozis, and A. Morrison, Johns Hopkins University, Baltimore; J. Kaye, Oregon Health Sciences University, Portland; D. Knopman, M. Prod'Homme, and L. Langley, University of Minnesota Hospital, Minneapolis; V. Kumar, University of Miami, Miami Beach, Fla.; R. Margolin and P. Brooks, Vanderbilt University, Nashville; J. Morris and E. Rubin, Washington University Medical Center, St. Louis; R. Petersen and L. Limbo, Mayo Clinic, Rochester, Minn.; E. Pfeiffer, University of South Florida Health Sciences Center, Tampa; M. Raskind and E. Peskind, Veterans Affairs Medical Center, Seattle; M. Sano, K. Marder, K. Bell, G. Dooneief, P. Schofield, M. Chun, A. Lawton, and J. Wilson, Columbia University, New York; F. Schmitt and W. Ashford, University of Kentucky, Lexington; L. Schneider, S. Pawluczyk, J. Olin, N. Taggart, and C. Ghoush, University of Southern California, Los Angeles; W. Scrittmatter and S. Wyne, Duke University, Durham, N.C.; L. Thal, W. Samuel, J. Corey Bloom, D. Galasko, D. Bower, and V. Rice, University of California at San Diego, La Jolla; P. Whitehouse, A. Lerner, K. Horner Fedor, P. Hedera, M. Patterson, M. Sanders, and C. Zadorozny, University Hospitals of Cleveland, Cleveland. Members of the data-monitoring and data-coordinating staff: J. Bochenek, L. Simon, B. White, S. Jin, J. Jeong, L. Berkman, J. Mackell, and M. Schittini. Members of the safety-monitoring committee: E. Jackson, P. Tariot, and T. Sunderland.

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# EFFECTS OF TOCOPHEROL AND DEPRENYL ON THE PROGRESSION OF DISABILITY IN EARLY PARKINSON'S DISEASE

THE PARKINSON STUDY GROUP*

**Abstract** *Background and Methods.* In 1987 we began a multicenter controlled clinical trial of deprenyl (a monoamine oxidase inhibitor) and tocopherol (a component of vitamin E that traps free radicals) in the treatment of early Parkinson's disease. We randomly assigned 800 patients to one of four treatments: placebo, active tocopherol and deprenyl placebo, active deprenyl and tocopherol placebo, or both active drugs. The primary end point was the onset of disability prompting the clinical decision to begin administering levodopa. An interim analysis showed that deprenyl was beneficial (N Engl J Med 1989;321:1364-71). We report the results of tocopherol treatment after a mean (±SD) follow-up of 14±6 months, as well as the follow-up results for deprenyl.

*Results.* There was no beneficial effect of tocopherol or any interaction between tocopherol and deprenyl. The beneficial effects of deprenyl, which occurred largely during the first 12 months of treatment, remained strong and significantly delayed the onset of disability requiring levodopa therapy (hazard ratio, 0.50; 95 percent confidence interval, 0.41 to 0.62; P<0.001). The difference in the estimated median time to the end point was about nine months. The ratings for Parkinson's disease improved during the first three months of deprenyl treatment; the motor performance of deprenyl-treated patients worsened after the treatments were withdrawn.

*Conclusions.* Deprenyl (10 mg per day) but not tocopherol (2000 IU per day) delays the onset of disability associated with early, otherwise untreated Parkinson's disease. The action of deprenyl that accounts for its beneficial effects remains unclear. (N Engl J Med 1993;328:176-83.)

A VARIETY of oxidative mechanisms, involving the activity of monoamine oxidase and the formation of free radicals, have been implicated in the degeneration of neurons in the substantia nigra.[1] The possible role of such mechanisms in the pathogenesis of Parkinson's disease has led to clinical trials aimed at slowing the progressively disabling course of this illness. Deprenyl (selegiline or phenylisopropylmethylpropynylamine) is a selective and irreversible inhibitor of type B monoamine oxidase when administered in a dosage of 10 mg per day.[2,3] α-Tocopherol, a biologically active component of vitamin E, attenuates the effects of lipid peroxidation by trapping free radicals.[4,5]

The multicenter controlled clinical trial Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) was carried out to determine whether long-term therapy with deprenyl or tocopherol would extend the length of time before advancing disability requires the initiation of levodopa therapy in patients with early, untreated Parkinson's disease.[1] An interim analysis of this trial, prompted by independent monitoring and based on the observation of 800 patients for a mean (±SD) of 12±5 months, indicated that deprenyl reduced the risk of disability requiring levodopa therapy by approximately 50 percent.[5] However, it was unclear whether the effects of deprenyl would be sustained or whether deprenyl resulted in short-term amelioration of clinical features (symptomatic effect), a slowing of underlying nigral degeneration (protective effect), or both mechanisms. This report extends the analysis of the DATATOP clinical trial to include 14±6 months of observation and a modification of the protocol based on the interim analysis, and addresses the independent and interactive effects of tocopherol and deprenyl.

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*The members of the Parkinson Study Group who conducted the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism (DATATOP) trial and wrote this report are listed in the Appendix. The preparation of the manuscript was overseen by the DATATOP Steering Committee: Ira Shoulson, M.D. (principal investigator), University of Rochester, Rochester, N.Y.; Stanley Fahn, M.D. (co-principal investigator), Columbia-Presbyterian Medical Center, New York; David Oakes, Ph.D. (chief biostatistician), and Karl Kieburtz, M.D. (medical director), University of Rochester; Anthony Lang, M.D., Toronto Hospital, Toronto; J. William Langston, M.D., California Parkinson's Foundation, San Jose; Peter LeWitt, M.D., Sinai Hospital, Detroit; C. Warren Olanow, M.D., University of South Florida, Tampa; John B. Penney, M.D., University of Michigan, Ann Arbor; Caroline Tanner, M.D., Rush-Presbyterian-St. Luke's Medical Center, Chicago; and Alice Rudolph, Ph.D. (senior study coordinator), and Rita M. Pelusio, M.S.Ed. (program manager), University of Rochester.

## METHODS

The methods used in the DATATOP trial, including a description of the design, organization, recruitment of subjects, data acquisition and management, statistical methods, and interim results, have been reported in detail elsewhere[1,6] and are summarized below.

### Enrollment and Follow-up

Eight hundred untreated patients who had had Parkinson's disease (stage I or II) for less than five years and who met other eligibility criteria[1] were enrolled between September 3, 1987, and November 15, 1988. They were randomly assigned according to a two-by-two factorial design[7] to one of four treatment groups: tocopherol placebo and deprenyl placebo; tocopherol (2000 IU per day) and deprenyl placebo; deprenyl (10 mg per day) and tocopherol placebo; and deprenyl (10 mg per day) and tocopherol (2000 IU per day). The process of randomization was designed to ensure that each investigator had an approximate numerical balance of subjects in the four groups.[6] The subjects took 1000-IU capsules of racemic *dl*-α-tocopherol or identical-appearing placebo capsules (Hoffmann-LaRoche, Nutley, N.J.) and 5-mg tablets

of L-deprenyl or identical-appearing tablets of placebo (Somerset Pharmaceuticals, Tampa, Fla.) twice daily with morning and evening meals.

The subjects were reevaluated 1 month and 3 months after randomization and approximately every 3 months thereafter, for a planned maximum of 24 months of follow-up. At each visit, the subjects were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS), including its motor, mental, and activities-of-daily-living components.[8] Evaluation with the Hamilton Depression Scale[9] was carried out at base line, at one and three months, and at six-month intervals thereafter. The procedures for monitoring surveillance laboratory tests and compliance are described elsewhere.[1,6]

### End Points

The primary end point of the trial occurred when, in the judgment of the enrolling investigator, a subject reached a level of functional disability sufficient to warrant the initiation of levodopa therapy.[1] Thereupon, the experimental treatments were withdrawn and investigators and subjects were kept unaware of the treatment assignments; the subjects underwent final evaluations approximately 30 days later.

### Modification of the Protocol

An independent monitoring committee recommended (February 11, 1989) an interim analysis[6] of the effect of deprenyl, which included follow-up data obtained through May 20, 1989, when investigators were first informed of the interim results. The subjects were first advised of the interim findings after their scheduled follow-up visits conducted between July 31, 1989, and December 19, 1989.

All actively participating subjects who had not reached the primary end point provided informed consent for the modification of the trial that followed the interim analysis. Under the revised protocol, additional follow-up evaluations of these subjects were performed approximately one and two months after experimental treatments were withdrawn by tapering the dosages over a one-week period. Treatment with deprenyl (10 mg per day) could be started during the two months after treatment was withdrawn if the investigator determined that features of Parkinson's disease had worsened sufficiently as a consequence of the withdrawal of experimental treatments. All subjects, coordinators, and investigators were kept unaware of the treatment assignments throughout this modified phase of the trial.

### Statistical Analysis

In accordance with the intention-to-treat principle,[10] statistical analyses included all 800 subjects who were randomly assigned to the four treatment groups. All P values were two-tailed. The primary analysis used methods for evaluating survival[11] to account for the varying lengths of follow-up among subjects who reached the end point, those who withdrew from the trial before reaching the end point, and those still being followed who had not reached the end point. The cumulative probabilities of reaching the end point were estimated with the method of Kaplan and Meier[12]; data on subjects who withdrew from the study were censored as of their date of withdrawal. The end-point comparisons used Pearson's chi-square statistic,[13] the stratified log-rank test,[14] and Cox's proportional-hazards regression model,[15] with the identity of the participating investigator entered as a stratification factor. The risk among subjects receiving an active treatment (deprenyl or tocopherol), relative to that among subjects not receiving that treatment, was expressed as a hazard ratio — that is, the ratio of the risk per unit of time until the end point was reached among subjects assigned to active treatment to the corresponding risk among subjects not assigned to that treatment.

The differences among the four treatment groups with respect to adverse effects reported after base line were evaluated by chi-square statistics.[13] The rates of disease progression and the changes in the scores of the UPDRS and the Hamilton Depression Scale were evaluated by analysis of variance,[15] with adjustment for investigator effects. Follow-up variables were analyzed to determine the main effects of deprenyl and tocopherol as well as interactions between these drugs.

## Results

### Comparability of Treatment Groups and Adverse Events

The four treatment groups did not differ significantly in the variables measured at base line, including age, sex, ratings on the UPDRS and Hamilton Depression Scale, any previous levodopa treatment, time from the onset of illness to randomization, level of education, and employment status.

The occurrence of adverse symptoms, other medical conditions, and abnormal laboratory results was generally infrequent and uniform among all treatment groups. Of the 63 symptoms of moderate or serious severity reported to have occurred at least once, regardless of any perceived relation to experimental treatments or Parkinson's disease, only nausea occurred disproportionately (in one subject taking placebo only, none taking tocopherol and placebo, two taking deprenyl and placebo, and six taking both drugs; nominal P = 0.045, deprenyl).

Of the 17 other medical conditions reported to have occurred at least once, regardless of any perceived relation to the experimental treatments or Parkinson's disease, only musculoskeletal injuries and cardiac arrhythmias occurred disproportionately (injuries in 5 subjects taking placebo only, 6 taking tocopherol and placebo, 18 taking deprenyl and placebo, and 11 taking both drugs; nominal P = 0.007, deprenyl; arrhythmias: 1 subject taking placebo, none taking tocopherol and placebo, 4 taking deprenyl and placebo, and 4 taking both drugs; nominal P = 0.045, deprenyl). The cardiac arrhythmias were not considered life-threatening and included increased premature ventricular contractions (one subject taking placebo only and one taking both drugs), supraventricular tachycardia (one taking deprenyl and placebo and one taking both drugs), and bradycardia with varying degrees of atrioventricular block (three taking deprenyl and placebo and two taking both drugs). No significant treatment-related changes in blood pressure or pulse recordings were found during the study.

Of the clinically important laboratory abnormalities found on the battery of 41 surveillance tests, only abnormal elevation of serum aminotransferase levels was found to be a significant treatment effect. Aspartate aminotransferase levels exceeding 36 U per liter in men and 34 U per liter in women occurred in 10 subjects taking placebo only, 3 taking tocopherol and placebo, 20 taking deprenyl and placebo, and 8 taking both drugs (P = 0.028, deprenyl; and P = 0.005, tocopherol); alanine aminotransferase levels exceeding 43 U per liter in men and 34 U per liter in women occurred in 10 subjects taking placebo only, 4 taking tocopherol and placebo, 24 taking deprenyl and placebo, and 7 taking both drugs (P = 0.016, deprenyl; and P = 0.001, tocopherol). Elevations of alanine aminotransferase levels exceeding 150 percent of base-line values on more than one follow-up visit were

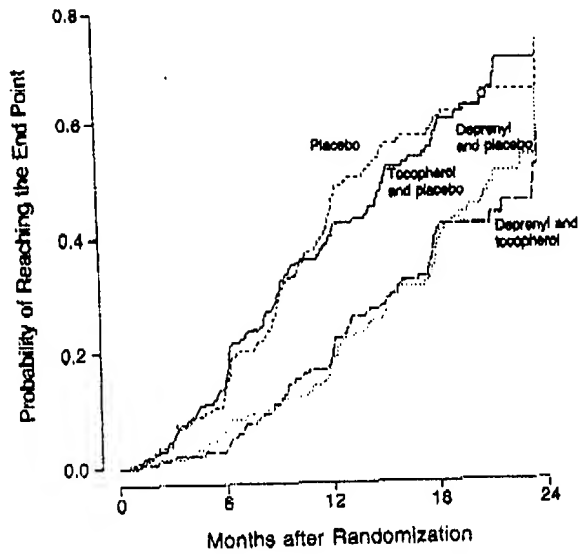
found in only two subjects (one taking deprenyl and placebo and one taking both drugs). Adverse events prompted emergency disclosure of the treatment assignments of two subjects (one taking deprenyl and placebo and one taking both drugs) in whom cancer developed and one subject taking both drugs who had hallucinations. No subjects died while participating in this phase of the study.

Compliance in taking experimental medications was excellent among all treatment groups. The overall compliance rate, as a percentage of the doses dispensed that were actually taken, ranged from 97.9 to 99.5 percent for both tocopherol and deprenyl. The results of urine testing for amphetamine and methamphetamine during the follow-up visits agreed well with the treatment assignments, ranging from 95 to 100 percent agreement among subjects not assigned to deprenyl and from 86 to 95 percent among those assigned to deprenyl. The distribution of serum tocopherol concentrations exceeding 2.0 mg per deciliter (46 μmol per liter) during the follow-up visits also matched the treatment assignments, ranging from 81 to 100 percent agreement among subjects not assigned to tocopherol and from 78 to 90 percent among those assigned to tocopherol.

### End Points

Table 1 compares the status according to treatment group, as of the last evaluation during experimental treatments, of the 376 subjects who reached the primary end point, the 57 subjects who withdrew from the study before reaching the end point, and the 367 subjects who were still being followed and had not reached the end point.

Tocopherol treatment (regardless of deprenyl administration) did not reduce the probability of reaching the end point (hazard ratio, 0.91; 95 percent confidence interval, 0.74 to 1.12; P = 0.35), and the hazard ratios for tocopherol remained homogeneous throughout the maximal period of follow-up (24 months). Tocopherol alone did not significantly reduce the risk of reaching the end point, as compared with double placebo (hazard ratio, 0.92; 95 percent confidence interval, 0.70 to 1.22; P = 0.57). There was no interaction between deprenyl and tocopherol (P = 0.97).




| | | | | | |
|---|---|---|---|---|---|
| Placebo | 199 | 164 | 102 | 60 | 3 |
| Tocopherol and placebo | 202 | 165 | 109 | 48 | 0 |
| Deprenyl and placebo | 202 | 181 | 153 | 81 | 3 |
| Deprenyl and tocopherol | 197 | 184 | 143 | 72 | 8 |

Figure 1. Kaplan–Meier Estimate of the Cumulative Probability of Reaching the End Point, According to Treatment Group.

The hazard ratio for the comparison of subjects taking deprenyl (with placebo or tocopherol) with subjects not taking deprenyl (placebo only or tocopherol with placebo) with respect to the risk of reaching the end point per unit of time is 0.50 (P<0.001; 95 percent confidence interval, 0.41 to 0.62). The period of analysis was the time from base line to the last evaluation during treatment. The number of subjects evaluated in each group is shown under each time point.

Kaplan–Meier plots (Fig. 1) of the probability of reaching the end point of the study differed significantly between subjects assigned to deprenyl (with placebo or tocopherol) and those not assigned to deprenyl (those taking placebo alone or placebo and tocopherol) (hazard ratio, 0.50; 95 percent confidence interval, 0.41 to 0.62; P<0.001). The projected median lengths of time to reaching the end point were 510 days for the subjects who were assigned to deprenyl and 454 days for the subjects who were not assigned to deprenyl, representing an approximate difference of almost 9 months.

Although the overall hazard ratio of 0.50 for deprenyl treatment was significant, the hazard ratio did not remain constant during the 24 months of follow-up; it increased from 0.35 (95 percent confidence interval, 0.21 to 0.58) during the first 6 months to 0.38 (95 percent confidence interval, 0.27 to 0.54) during the second 6 months, to 0.77 (95 percent confidence interval, 0.52 to 1.15) during the third 6 months, and to 0.86 (95 percent confidence interval, 0.45 to 1.66) after

Table 1. Status of the Subjects during the Study Period, According to Treatment Group.*

| Status | Placebo | Tocopherol and Placebo | Deprenyl and Placebo | Deprenyl and Tocopherol | Total |
|---|---|---|---|---|---|
| | | | *no. of subjects* | | |
| Reached end point | 113 | 109 | 80 | 74 | 376 |
| Withdrew before reaching end point | 14 | 16 | 12 | 15 | 57 |
| Remained in trial without reaching end point | 72 | 77 | 110 | 108 | 367 |
| Total | 199 | 202 | 202 | 197 | 800 |

*Values are those recorded just before the withdrawal of experimental treatments. The subjects were followed for a mean (±SD) of 14±6 months after randomization.

18 months. According to Cox's test,[16] these hazard ratios were significantly heterogeneous (P = 0.008). The Kaplan–Meier plots for the first 18 months after randomization were virtually identical to the plots reported in the preliminary analysis[6]; thereafter, the probabilities of reaching the end point did not continue to diverge. Subjects assigned to deprenyl benefited from treatment irrespective of their base-line characteristics. There were no significant differences in treatment effects in relation to the enrolling investigator, the age of the subject, or the date of entry of the subject.

The 367 subjects who did not reach the end point were withdrawn from experimental treatments and evaluated approximately one and two months later. During the two months after treatment was withdrawn, 4 subjects (2 taking double placebo, 1 taking tocopherol and placebo, and 1 taking deprenyl and placebo) reached the primary end point, 1 taking both drugs left the trial, and 52 were judged by the investigator to have an increase in the severity of Parkinson's disease and were given deprenyl. There was no evidence of differences among the treatment groups in the rate of early deprenyl administration (12 of 72 subjects taking double placebo, 17 percent; 13 of 77 taking tocopherol and placebo, 17 percent; 19 of 110 taking deprenyl and placebo, 17 percent; and 8 of 108 taking both drugs, 7 percent; P = 0.12).

### Secondary Response Variables

Table 2 shows the average rate of decline from base-line values for the UPDRS variables in all subjects completing at least a six-month evaluation, regardless of whether they reached the end point. There were no significant differences in the rate of change in secondary response variables between subjects assigned to tocopherol and those not assigned to tocopherol. The average rate of decline in all UPDRS variables was significantly slower in subjects taking deprenyl (with placebo or tocopherol) than in subjects not taking deprenyl (those taking placebo alone or tocopherol and placebo).

For subjects who did not reach the end point (survivors), the rates of decline in UPDRS variables were calculated from base line (before the initiation of experimental treatments) to the evaluation that occurred approximately two months after the withdrawal of treatment (Table 2). Survivors assigned to deprenyl had a significantly slower decline in total UPDRS scores than did their counterparts who were not assigned to deprenyl. For subjects who reached the end point, most of the decline in UPDRS scores typically occurred immediately before the determination that the end point had been reached,[17] and there were no significant differences between treatment groups in the motor ratings on the UPDRS at the time that the end point was reached (data not shown).

Table 3 shows the changes in the ratings on the UPDRS and Hamilton Depression Scale from base line in all subjects who completed follow-up evaluations after one and three months. Significant changes during the first three months of treatment (the "wash-in" period) favoring the subjects taking deprenyl occurred in all UPDRS variables at one and three months. No significant short-term changes in UPDRS ratings were found that favored the subjects taking tocopherol.

When the subjects in each treatment group were divided into those who had an initial improvement in the total UPDRS score between base line and one month (a total of 407 subjects; 215 assigned to deprenyl and 192 not assigned to deprenyl) and those who had a decline or no change in the score (a total of 379 subjects; 178 assigned to deprenyl and 201 not assigned to deprenyl), the differences in the rate at which the end point was reached favored those as-

Table 2. Average Annual Rate of Decline in UPDRS Ratings.*

| UPDRS Component | Placebo | Tocopherol and Placebo | Deprenyl and Placebo | Deprenyl and Tocopherol | P Value† |
|---|---|---|---|---|---|
| | | | *rating (no. of subjects)* | | |
| Total (all components) | | | | | |
| All subjects | 14.02±12.32 (175) | 15.16±16.12 (178) | 7.00±10.76 (190) | 7.28±11.11 (182) | <0.001 |
| Survivors | 5.74±5.64 (57) | 5.57±5.98 (63) | 3.63±4.32 (89) | 3.60±5.35 (96) | <0.001 |
| Mental | | | | | |
| All subjects | 0.69±1.72 (176) | 0.71±2.03 (178) | 0.12±1.20 (191) | 0.04±1.10 (182) | <0.001 |
| Survivors | 0.02±0.94 (57) | 0.02±0.74 (63) | +0.07±0.75 (89)‡ | +0.03±0.76 (96)‡ | 0.599 |
| Motor | | | | | |
| All subjects | 8.91±8.41 (175) | 9.80±10.81 (178) | 4.90±7.61 (190) | 4.87±8.01 (182) | <0.001 |
| Survivors | 3.62±3.74 (57) | 3.92±4.47 (63) | 2.66±3.22 (89) | 2.51±3.86 (96) | 0.002 |
| Activities of daily living | | | | | |
| All subjects | 4.40±4.34 (176) | 4.65±5.81 (178) | 2.01±3.94 (190) | 2.38±3.69 (182) | <0.001 |
| Survivors | 2.10±2.28 (57) | 1.62±2.02 (63) | 1.04±1.95 (89) | 1.13±2.16 (96) | 0.002 |

*Plus–minus values are means ±SD. In this analysis the term "all subjects" refers to those who completed at least a six-month evaluation regardless of whether they reached the end point (the rate of decline in these subjects was calculated from the base-line period to the last evaluation during treatment), and the term "survivors" refers to those who did not reach the end point and who did not require early initiation of deprenyl by the end of the two-month period after the withdrawal of treatments (the rate of decline in these subjects was calculated from the base-line period to the end of the two-month withdrawal period). The "all subjects" group was followed for a mean (±SD) of 16±6 months from randomization, and the "survivors" for 21±4 months.

†P values were calculated by analysis of variance and indicate the main effect of deprenyl.

‡Instead of declining, the score improved.

Table 3. Changes in the Ratings on the UPDRS and Hamilton Depression Scale during the Initial Three Months of Treatment (Wash-in) and the Two Months after Withdrawal of Treatments (Washout).*

| Scale | Placebo | Tocopherol and Placebo | Deprenyl and Placebo | Deprenyl and Tocopherol | P Value† |
|---|---|---|---|---|---|
| | | *rating (no. of subjects)* | | | |
| **UPDRS component** | | | | | |
| Total (all components) | | | | | |
| 1-Mo wash-in | 0.11±5.98 (195) | −0.37±6.16 (198) | 2.07±6.36 (199) | 1.30±6.65 (194) | <0.001 |
| 3-Mo wash-in | −1.34±6.70 (181) | −1.94±7.31 (184) | 1.56±7.04 (195) | 1.42±7.35 (186) | <0.001 |
| 1-Mo washout | −1.23±5.97 (69) | −0.91±5.10 (76) | −2.25±5.73 (106) | −2.04±5.36 (106) | NS |
| 2-Mo washout | −0.48±5.72 (57) | −0.53±6.26 (63) | −3.24±4.95 (87) | −3.10±6.21 (95) | <0.001 |
| Mental | | | | | |
| 1-Mo wash-in | 0.19±1.21 (195) | 0.02±1.13 (198) | 0.28±0.97 (200) | 0.32±1.23 (194) | 0.020 |
| 3-Mo wash-in | 0.10±1.21 (181) | 0.02±1.17 (184) | 0.27±1.15 (196) | 0.40±1.18 (186) | 0.001 |
| 1-Mo washout | −0.12±0.96 (69) | −0.11±1.28 (76) | −0.11±0.93 (106) | 0.03±1.02 (106) | NS |
| 2-Mo washout | 0.18±1.07 (57) | 0.00±1.02 (63) | −0.09±0.86 (87) | −0.04±1.05 (95) | NS |
| Motor | | | | | |
| 1-Mo wash-in | 0.01±4.33 (195) | −0.28±4.73 (198) | 1.40±4.82 (199) | 0.66±4.95 (194) | <0.001 |
| 3-Mo wash-in | −0.76±4.89 (181) | −1.38±5.38 (184) | 0.93±5.49 (195) | 0.78±5.43 (186) | <0.001 |
| 1-Mo washout | −0.26±4.43 (69) | −0.49±3.87 (76) | −1.47±4.79 (106) | −1.27±4.16 (106) | 0.042 |
| 2-Mo washout | −0.20±4.65 (57) | −0.09±4.95 (63) | −2.24±3.93 (87) | −2.18±4.87 (95) | <0.001 |
| Activities of daily living | | | | | |
| 1-Mo wash-in | −0.09±2.36 (195) | −0.12±2.30 (198) | 0.40±2.32 (199) | 0.31±2.26 (194) | 0.005 |
| 3-Mo wash-in | −0.68±2.69 (181) | −0.58±2.67 (184) | 0.36±2.57 (195) | 0.24±2.71 (186) | <0.001 |
| 1-Mo washout | −0.86±2.81 (69) | −0.29±2.14 (75) | −0.67±1.92 (106) | −0.80±2.19 (106) | NS |
| 2-Mo washout | −0.46±2.16 (57) | −0.44±2.37 (62) | −0.91±2.35 (87) | −0.87±2.38 (95) | NS |
| **Hamilton Depression Scale** | | | | | |
| 1-Mo wash-in | 0.02±2.86 (194) | −0.21±2.60 (198) | −0.13±3.13 (200) | 0.58±2.87 (193) | NS |
| 3-Mo wash-in | −0.20±2.77 (181) | −0.46±3.17 (183) | 0.15±2.75 (194) | 0.38±3.27 (186) | 0.007 |
| 1-Mo washout | −0.52±2.73 (69) | −0.48±3.13 (75) | −0.30±2.07 (103) | −0.10±2.18 (105) | NS |
| 2-Mo washout | −0.68±1.92 (57) | −0.41±2.06 (63) | −0.23±2.45 (86) | −0.31±2.49 (95) | NS |

*Plus–minus values are means ±SD. Wash-in values represent the changes in scores between base line and follow-up visits at one and three months during treatment. Washout values represent the changes in scores among subjects who had not reached the end point (survivors), calculated for the interval between the last visit during treatment and the visits one and two months after the withdrawal of treatment. Subjects who required treatment with deprenyl during the two-month withdrawal phase were included in the analyses of the washout values. Positive values indicate improvement, and negative values indicate worsening of disease.

†P values were calculated by analysis of variance and indicate the main effect of deprenyl. NS denotes not significant.

signed to deprenyl in both subgroups (subgroup with improvement: hazard ratio, 0.55; 95 percent confidence interval, 0.40 to 0.75; P<0.001; subgroup without improvement: hazard ratio, 0.53; 95 percent confidence interval, 0.39 to 0.73; P<0.001) (Fig. 2). The beneficial effect of deprenyl in reducing the risk of reaching the primary end point persisted even when this analysis was carried out with data collected after the one-month visit (data not shown) and when the subjects assigned to deprenyl who did not improve were compared with subjects not assigned to deprenyl who did improve (hazard ratio, 0.56; 95 percent confidence interval, 0.40 to 0.78; P<0.001).

Among subjects who reached the end point, the mean changes in UPDRS ratings between the evaluation at the end point and the final evaluation one month later were slight, and the differences between the treatment groups were not significant except for a relative improvement (P = 0.006) in the mental component of the UPDRS in subjects not assigned to deprenyl.

Among the subjects who did not reach the end point and who were withdrawn from experimental treatments in accordance with the modification of the trial protocol, slight worsening of the motor component of the UPDRS was found one month (P = 0.042) and two months (P<0.001) after the withdrawal of treatments in the subjects assigned to deprenyl as compared with the subjects not assigned to deprenyl (Table 3). The disproportionate worsening of motor performance was largely attributable to changes in scores for tremor and rigidity. There were no significant treatment-related effects due to withdrawal on the mental or activities-of-daily-living components of the UPDRS or on the Hamilton Depression Scale.

## Discussion

### Effects of Tocopherol on Primary and Secondary Response Variables

Our clinical trial revealed no evidence of any beneficial effect of α-tocopherol (2000 IU per day) in either slowing functional decline or ameliorating the clinical features of Parkinson's disease. The failure of tocopherol to influence the progression of Parkinson's disease in this study does not preclude the potential effectiveness of other antioxidants. Treatment with tocopherol, which traps peroxyl radicals and interrupts the chain reaction of lipid peroxidation, may be less effective than interventions that prevent the formation of cytotoxic radicals and the initiation of lipid peroxidation.[5] It is also possible that inadequate amounts of tocopherol accumulated in the central nervous system in our subjects.

### Effects of Deprenyl on Primary and Secondary Response Variables

Our previous findings of a substantial benefit of deprenyl in delaying the onset of disability associated

with Parkinson's disease have been confirmed by the findings in this extended period of observation. The results translate into a delay of almost nine months in the development of disability requiring levodopa therapy. These benefits were associated with a slight improvement in motor performance after deprenyl treatment was begun and a slight worsening after it was withdrawn. The benefits of deprenyl with respect to the primary end point of disability were found in all subjects regardless of their base-line characteristics and are supported by a slowing of the rate of decline of the UPDRS scores (Table 2). The effect of deprenyl on all response variables was the same among patients who received tocopherol and those who did not.

#### Mechanisms of Deprenyl Effects

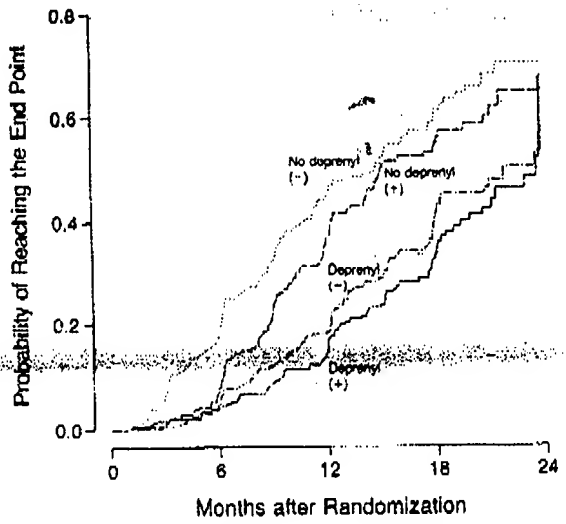
Our data support our previous findings that deprenyl is well tolerated and slows the functional decline of otherwise untreated subjects with early Parkinson's disease. The pattern of the survival curves comparing subjects who received deprenyl with those who did not receive it showed initial sharp divergence followed by approximately constant separation. Our extended observations, which included a two-month period without treatment, indicate that deprenyl produces a slight but sustained improvement in the clinical ratings of Parkinson's disease.

The improvement in the UPDRS scores after the initiation of deprenyl and the worsening of the UPDRS motor scores during the two months after withdrawal (Table 3) suggest that the observed benefit of deprenyl in delaying disability is partly related to a symptomatic amelioration of Parkinson's disease. On the other hand, the superior survival with respect to the primary end point even among deprenyl-treated subjects who initially had no improvement in total UPDRS scores (Fig. 2) and the overall persisting benefit (as compared with base-line status) among deprenyl-treated subjects who did not reach the end point and who did not require deprenyl during the two months after withdrawal (Table 2) suggest a protective influence. There was no evidence that deprenyl had appreciable antidepressant effects during this extended period of observation.

Uncontrolled studies suggest that deprenyl may increase the life span of patients with advanced Parkinson's disease[18,19] and retard the death of nigral neurons.[20] The design of our clinical trial was based on earlier studies indicating that deprenyl did not by itself lead to symptomatic improvement in patients with early Parkinson's disease.[21,22] The small but definite ameliorating influence of deprenyl that we observed on the motor ratings of Parkinson's disease hampers a clear-cut detection of potentially protective actions of this monoamine oxidase inhibitor.

#### Adverse Effects of Treatment

In keeping with our interim report,[6] the adverse effects of tocopherol and deprenyl were infrequent and not serious. The rare occurrence of cardiac arrhythmias among deprenyl-treated subjects is unexplained,




| | | | | | |
|---|---|---|---|---|---|
| No deprenyl (−) | 201 | 154 | 98 | 48 | 1 |
| No deprenyl (+) | 192 | 173 | 112 | 50 | 2 |
| Deprenyl (−) | 178 | 163 | 129 | 70 | 7 |
| Deprenyl (+) | 215 | 202 | 167 | 83 | 4 |

Figure 2. Kaplan–Meier Estimate of the Cumulative Probability of Reaching the End Point, According to Treatment with Deprenyl or without Deprenyl and to the Presence (+) or Absence (−) of Improvement in the One-Month Total UPDRS Score.

The period of analysis was the time from base line to the last evaluation during treatment. The number of subjects evaluated in each group is shown under each time point. See the Results section for hazard ratios and P values.

but this complication may be related to the monoaminergic effects of the parent compound and its active metabolites.[3] The infrequent occurrence of deprenyl-related elevations of serum aspartate aminotransferase and alanine aminotransferase levels has been reported previously[6,23] and seems to reflect clinically unimportant effects on hepatic or muscle enzymes. Although adverse effects on mental status were rare among our otherwise untreated subjects, deprenyl is known to cause untoward mental changes in patients with Parkinson's disease who are treated concurrently with levodopa or other drugs that enhance dopaminergic activity.[8]

#### Therapeutic Recommendations

In contrast to the findings from an uncontrolled pilot study,[24] our larger controlled study does not support the use of tocopherol at a dosage of 2000 IU per day in patients who have early Parkinson's disease. The use of deprenyl in a dose of 10 mg per day as monotherapy for early Parkinson's disease delays the development of disability requiring levodopa therapy. Therefore, deprenyl should be considered among the available therapeutic options for the initial treatment of early Parkinson's disease.

#### Comparison of Present Results with Earlier Results

The effects of deprenyl demonstrated by our present analysis remain strong, but they have been less dramatic over the extended period of observation than the effects we reported previously.[6] The evidence

that deprenyl ameliorates some of the clinical features of Parkinson's disease is clearer in this analysis than in our previous report or in smaller controlled studies carried out by other investigators.[25-29] Our ability to detect small clinical effects is related to the large study sample, the extended period of observation, and the longer period of withdrawal from experimental treatments among subjects who had not reached the end point of disability. Previous studies have suggested that deprenyl has a protective effect,[6,25,26,29] but this assertion has not yet been established.

### Unresolved Issues and Future Investigations

Despite the lack of benefit of tocopherol in this trial, studies of other antioxidant agents in Parkinson's disease are still warranted. Examination of the effects of L-amphetamine metabolites of deprenyl[29,30] and of shorter-acting inhibitors of monoamine oxidase type B, such as lazabemide,[31] which are not metabolized to active compounds, may help clarify the action of deprenyl. Inhibitors of monoamine oxidase type A, the predominant intraneuronal form of this enzyme,[32,33] may also be of interest. The lack of validated biologic markers for the progression of Parkinson's disease hampers attempts to define the action of interventions in the treatment of this disorder.

In the present trial, despite the subjective nature of the primary end point and the large number of investigators, we have consistently found a beneficial effect of deprenyl.[34] The changes observed in the UPDRS variables supported this finding. The lack of conclusive evidence of a neuroprotective effect of deprenyl justifies further placebo-controlled trials of other promising agents in patients with early Parkinson's disease.

## Appendix

The following are participants in the DATATOP trial:

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Site Coordinators — R. Barter and B. Vetere-Overfield, Kansas City, Kans.; L. Gauger and T. Malapira, Tampa, Fla.; J. Dobson, Iowa City, Iowa; S. Atamian, M. Tennis, J.B. Cohen, G. Desclos, and E. Hollman, Boston; L. Denio, S. Huber, T. Woike, K. Zoog, R. Mendell, and K. Dudte, Columbus, Ohio; J. Behr, I.F. Gardiner, Rochester, N.Y.; M. Lannon, Providence, R.I.; J. Carter and S. Northrup, Portland, Oreg.; B. Kanigan, Saskatoon, Sask.; M. Turk and E. Landow, Charlottesville, Va.; P. Schlick and K. Mistura, Detroit; V.S. Carroll and J.A. Thelen, Chicago; C. Demong, Calgary, Alta.; L. Winfield and C. Moskowitz, New York; A. Ingenito, C. Sheldon, and L. Cornelius, Miami; D. Heiberg and C. Dunne, Houston; J. Brady, Ann Arbor, Mich.; C. Kierans, L. Belle-Scantlebury, and J. Duff, Toronto; H. Weber, Denver; D. Savoini, P. Lewis, and S.J. Kutner, San Jose, Calif.; P. Gray, Ottawa; C. Glaeske and R. Hofman, Omaha, Neb.; M.M. Pay and D. Salmon, San Diego, Calif.; F. McFaul and D. Amyot, Montreal; M. Bergen, New Brunswick, N.J.; L. McGee-Minnich, St. Louis; P. O'Donnell, Baltimore; and S. Ferrise and K. Shallow, Philadelphia.

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Biostatistics Center — Department of Biostatistics, University of Rochester Medical Center, Rochester, N.Y.: C. Odoroff (deceased) and D. Oakes (chief biostatisticians); M. McDermott and S. Eberly (biostatisticians); S. Plumb (lead programmer); and A. Watts, L. Yorkey, A. Choi, and K. Gerwitz (analyst–programmers).

Pharmacy Center — Strong Memorial Hospital, Rochester, N.Y.: P. Evans (chief pharmacist); and L. Dellapena and V. Singletary (pharmacy technicians).

Safety Monitoring Committee — R. Herndon (chair, January 1, 1987, to June 30, 1988), Portland, Oreg.; P. Tariot (chair, July 1, 1988, to present), Rochester, N.Y.; and E. Bell, R.C. Griggs, and W.J. Hall, Rochester, N.Y.

Scientific Advisory Committee — C.D. Marsden (chair), London; T.N. Chase, Bethesda, Md.; G. Cohen, J. Fleiss, and R. Mayeux, New York; L. Jacobs and A.J. Moss, Rochester, N.Y.; and E. Melamed, Tel Aviv, Israel.

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CSF Assay Center — Lafayette Clinic, Wayne State University, Detroit: M.P. Galloway (director); M. Kaplan (deceased), R. Lodhi, M.J. Keegan, B. Matthews, and E.A. Novak.

Deprenyl Metabolites Assay Center — Institute for Medical Research, San Jose, Calif.: I. Irwin (director).

Tocopherol Assay Center — Our Lady of Mercy Medical Center, Bronx, N.Y.: E. Norkus (director).

Specimen Repository — Department of Neurology, University of Rochester, Rochester, N.Y.: D. Flood (director), T. McNeill, N. Harary, and L. Koek.

Laboratory Surveillance Testing — SciCor Laboratories, Indianapolis: R.L. Creveling (director).

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